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The cyanoetylation of 5 amino tetrazole.

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Monterey, California: U.S. Naval Postgraduate School

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THE CYANOETHYLATION OF
5 AMINO TETRAZOLE

VANCE L. HARRIS

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OF 5 AMINO TETRAZOLE

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Vance L. Harris

THE CYANOETHYLATION
OF 5 AMINO TETRAZOLE

by

Vance L. Harris
//
Lieutenant, United States Navy

Submitted in partial fulfillment of
the requirements for the degree of

MASTER OF SCIENCE
IN
CHEMISTRY

United States Naval Postgraduate School
Monterey, California

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OF 5 AMINO 1ETRAZOLE

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IN

CHEMISTRY

from the

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ABSTRACT

Reactions were carried out leading to the addition of 5 amino tetrazole to one and more molecules of acrylonitrile. The effectiveness of various catalysts upon the addition was studied. The order of cyanoethylation at the acid and amine hydrogens of the 5 amino tetrazole was determined. The reaction products of the addition reactions were characterized.

The writer wishes to express his appreciation for the invaluable assistance rendered by Doctor Ronald A. Henry and Doctor William G. Finnegan of the Naval Ordnance Test Station during his introduction to the field of tetrazole chemistry, and to Professors John W. Schultz, George H. McFarlin, and Richard A. Reinhardt for their expert assistance and suggestions throughout the period that work on this thesis was continuing.

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1. Introduction

Acrylonitrile undergoes addition reactions with a wide variety of organic compounds containing an active hydrogen atom. In this addition the carbon-carbon double bond in acrylonitrile has about the same reactivity as the carbon-oxygen double bond in formaldehyde.⁴ The addition of a compound to the double bond of acrylonitrile results in the introduction into the compound of a cyanoethyl group, hence the reaction is referred to as cyanoethylation. Among the compounds having a labile hydrogen which add to acrylonitrile are:¹

- (a) Those containing the -NH-group, such as primary and secondary amines, amides, imides, and lactams.
- (b) Those containing one or more hydroxyl groups, such as alcohols and phenols.
- (c) Acidic compounds, such as hydrogen cyanide, hydrogen bromide and hypochlorous acid, but not the carboxylic acids.
- (d) Ketones and aldehydes having a -CH-, -CH₂-, or -CH₃ group adjacent to the carbonyl group.

These and many other classes of compounds undergo cyanoethylation but of primary interest here are groups (a) and (b) above, since the compound under consideration fits both of these categories having both an -NH₂ group and an acidic hydrogen other than carboxylic.

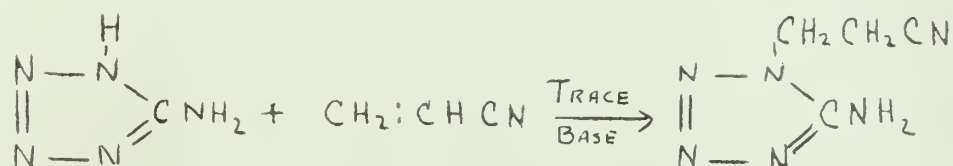
Some cyanoethylation reactions proceed without the aid of a catalyst, but most require an alkaline catalyst and a few require acidic catalysts. Useful catalysts are oxides, hydroxides, alkoxides, hydrides, and arides of sodium and potassium; the strongly basic quaternary ammonium hydroxides, and, in certain cases, acetic, sulfuric, or oxalic acid.

In general, amines add more readily to acrylonitrile than do other

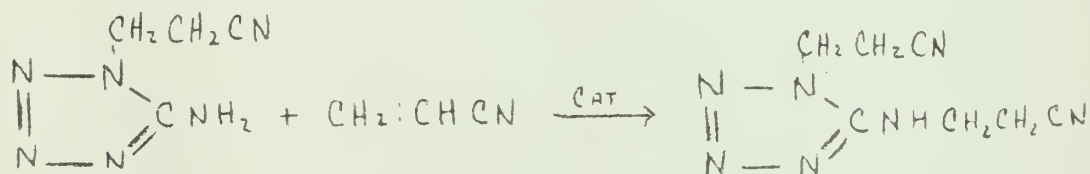
classes of compounds. Primary amines may react with two moles of acrylonitrile. Low temperatures favor the addition of one mole of amine while high temperature with an excess of acrylonitrile favors the addition to a second molecule of acrylonitrile.¹

The cyanoethylation reaction is reversible to the extent that many cyanoethylated compounds, when heated near their boiling points, will decompose to the starting compound and acrylonitrile or its polymer.¹

Briefly, the scheme of synthesis at the outset was as follows:



followed by:



first replacing the labile hydrogen of the acid, and next attempting to put a second molecule of acrylonitrile onto the amine group.

The first substitution was expected to give two isomeric forms of the addition product corresponding to addition at the 1- and 2- positions of the 5 aminotetrazole.

II. EXPERIMENTAL

(1) To a three necked flask fitted with stirrer, thermometer, and reflux condenser was added 0.1 mole of 5 amino tetrazole and 0.12 mole of acrylonitrile. Two drops of 50% sodium hydroxide in water were added and the mixture heated at reflux temperature for a period of four hours. No increase in temperature was observed upon mixing of the reactants and none after reflux temperature was reached. This indicated that no detectable reaction had taken place. The mixture remained heterogeneous throughout the period of reflux. The mixture was allowed to stand in the flask over the week end, after which the solid remaining in the flask was recrystallized from isopropyl alcohol. The crystals obtained melted 198°C , the melting point of 5 amino tetrazole, and a mixed melting point with pure 5 amino tetrazole gave no depression in the observed melting point. Longer periods of reflux also failed to yield any detectable addition product. The recovered 5 amino tetrazole in each case very nearly equalled the amount added at the beginning.

(2) In the second attempt to bring about the addition of the 5 amino tetrazole to acrylonitrile all the conditions remained the same as in (1) with the exception of the substitution of a small amount of sodium ethoxide for the sodium hydroxide. The results in this experiment were the same as those in (1). Sodium ethoxide was considered as a catalyst because of its partially organic nature, giving it greater solubility in the reagents used. The sodium ethoxide was freshly prepared from pure sodium and absolute ethyl alcohol.

(3) Experiment number (1) was repeated using increased quantities of aqueous sodium hydroxide as catalyst. From the reaction product a small amount of material was recovered melting in the range 49° - 50°C . Because



of its low melting point it seemed unlikely that this compound was the sodium salt of 5 amino tetrazole. However, further investigation, including reconversion to and recovery of the original 5 amino tetrazole, proved this compound to be the sodium salt of the acid. To explain the low, sharp melting point, it was considered that the salt must contain sufficient water of crystallization to bring about its own dissolution at about 50°C. This theory is borne out by the fact that after reaching more elevated temperatures (about 90°C) the melt again becomes solid and exhibits the behavior usually associated with the sodium salts of organic acids.

(L) Since sodium ethoxide and sodium hydroxide had been ineffective in catalyzing the reaction, it was decided next to try one of the strongly basic quaternary ammonium hydroxides. Since none of these were available it was necessary to prepare the hydroxide from the chloride of one of the quaternary ammonium compounds. To accomplish this, a stoichiometric amount of silver oxide was added, with heating and stirring, to an aqueous solution of tetramethyl ammonium chloride until precipitation of the silver halide was complete. The insoluble silver salt was then filtered off and the aqueous solution of the tetramethyl ammonium hydroxide was evaporated to as near dryness as was practicable (the quaternary ammonium hydroxides are hygroscopic). Next, the experiment of paragraph (1) was repeated, this time using a small amount of the tetramethyl ammonium hydroxide in place of the sodium hydroxide as catalyst. Reflux was allowed to continue until the mixture became homogeneous. This required about one hour. (In previous runs solution of the 5 amino tetrazole was never accomplished). Upon cooling, the reaction mixture solidified. Recrystallization from isopropyl alcohol yielded crystals melting in the range 94°-96°C. The compound

formed was found to be neutral (no reaction with sodium hydroxide as indicated by phenolphthalein) indicating that addition had taken place at the one or the two position of the 5 amino tetrazole. Since the reactants had been present in approximately stoichiometric amounts, and since, based upon the monosubstituted derivative, the yield was slightly better than ninety percent, it was concluded that the compound obtained had the following possible structures:



Repeated recrystallization failed to give any compound melting outside the range of 94° - 96°C , that is, no isomeric forms were separated.

(5) Upon obtaining the compound described in section (4) the same reactants were subjected to the same conditions with the exception that acetonitrile was substituted for acrylonitrile, and that the refluxing was carried out for several hours instead of one hour. Subjected to these conditions the 5 amino tetrazole was recovered unchanged, indicating that the reaction product of the previous experiment was due solely to the presence of acrylonitrile. Subsequent hydrolysis of the reaction product melting at 94° - 96°C yielded an acid and ammonia, indicating that the $-\text{CN}$ group had remained unchanged in the reaction of section (4) and was a part of the product molecule.

(() The reaction of (4) was repeated using the same reactants but with 0.24 moles of acrylonitrile and with reflux time extended to a period of four hours. The resulting reaction mixture was extracted with four 25 ml.



portions of dichloroethane (acrylonitrile polymer is only very slightly soluble in dichloroethane).¹¹ The dichloroethane was then extracted with cold water. From the water extract there was obtained crystals melting at 94-96°C. From the dichloroethane, after evaporation, there was obtained a quantity of clear, viscous oil. The crystals (M.P. 94-96°C) were identical with those of (4). Subsequent experiments showed the amount of oil obtained in this reaction was proportional to the time of reflux and the excess of acrylonitrile in the reaction mixture. After reflux times of the order of 20 hours no crystals melting at 94-96°C were recoverable from the reaction mixture. Upon standing, usually for a period of about five days, crystallization begins in the oil, rendering it opaque. Crystal growth proceeds very slowly and attempt to separate oil and crystals met with failure for the most part. Separation was finally accomplished in one case after an extended time had allowed crystal growth to proceed to the extent that the oil could be washed away from the embedded crystals with cold acetonitrile without dissolving the crystals. Even in this case the crystals were reduced to approximately one half their original size before being entirely freed of the oil. The crystals obtained melted in the range 116-118°C.

Acrylonitrile plus catalyst refluxed for extended periods yielded a polymer of acrylonitrile whose properties were not similar to those of the oil obtained in this reaction. A second run of the same reaction was made using an amount of acrylonitrile based upon addition of the fluorine tetra-zole to two molecules of acrylonitrile. As the acrylonitrile was removed by the reaction a point was reached where the temperature within the flask began to rise well above the boiling point of acrylonitrile and the mixture

decomposed rapidly, extruding itself up through and out of the reflux condenser onto the laboratory table. This action is characteristic of cyanoethylated amine groups.¹

(7) Since certain heterocyclic compounds add to acrylonitrile by the influence of acid catalysts, it was decided to try reacting the product obtained in (4) with acrylonitrile using glacial acetic acid as the catalysts. The same proportions and same conditions as in (1) were used except that five drops of glacial acetic acid was substituted for the tetramethyl ammonium hydroxide. After a period of refluxing in excess of eight hours, the 5 amino tetrazole was recovered unchanged.

(8) Into a thick walled tube was placed 0.1 mole of the reaction product of (4) (M.P. 94-96°C), and 15 ml. of acrylonitrile, five drops of glacial acetic acid was added and the contents chilled in a dry ice-acetone mixture. The tube was then evacuated and the tube sealed. The tube was maintained at a temperature of 120°C for two days, after which time the originally heterogeneous mixture was homogeneous. The reaction mixture was extracted several times with ethylene dichloride which, when evaporated, yielded a quantity of viscous oil. No unreacted material melting at 94-96°C was recovered.

(9) A quantity of 5 amino tetrazole was neutralized with sodium hydroxide, the solution evaporated and the crystals dried in an oven at 100°C for five hours. A tenth mole of the sodium salt, 0.2 mole of acrylonitrile, and a small amount of tetramethyl ammonium hydroxide were placed in a three necked flask fitted with stirrer, thermometer, and reflux condenser. The mixture was refluxed for a period of ten hours, after which time the reaction mixture had become homogeneous. The reaction mixture



was dissolved in water and a tenth mole of AgNO_3 in distilled water was added, yielding a dense, yellowish precipitate. The precipitate was dried, ground, and washed with a large volume of distilled water several times. The salt was then treated with hydrogen sulfide until conversion to silver sulfide was complete. The mixture was then filtered and the filtrate evaporated, yielding a clear, viscous oil with acidic properties.

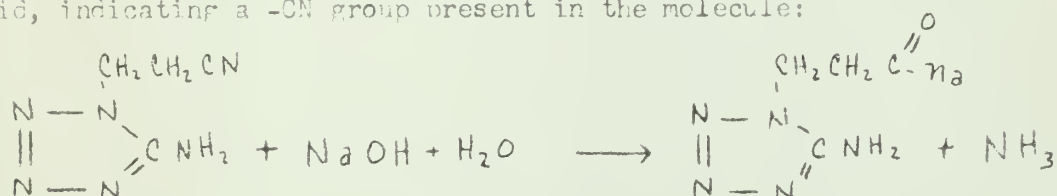
III CHARACTERIZATION

The first attempts to characterize reaction products were directed toward the compound resulting from (4) of the previous section. The compound was neutral; therefore, if cyanoethylation had taken place, a cyanoethyl group must have gone into the 1- or 2- position, replacing the acidic hydrogen:

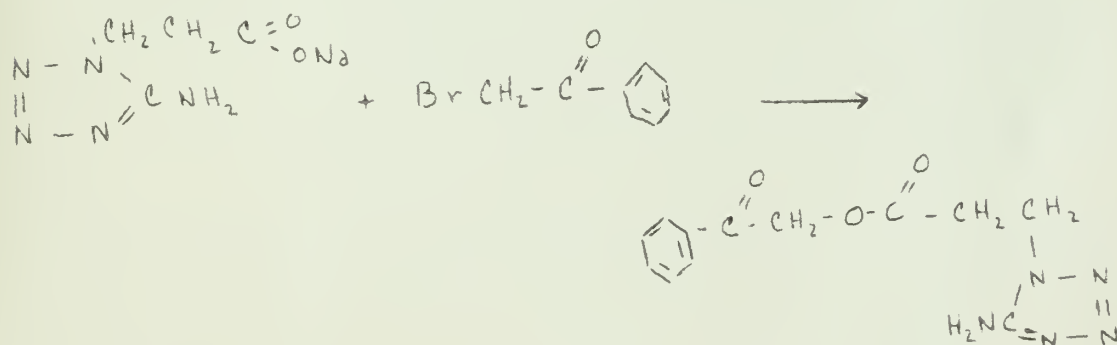


Reactions carried out in an attempt to characterize the compound follow.

(1) Hydrolysis of the compound with sodium hydroxide yielded ammonia and an acid, indicating a -CN group present in the molecule:

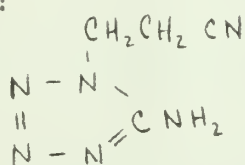


Attempts were made to isolate the free acid resulting from treatment of the hydrolysis mixture with hydrochloric acid, but without success. The acid appeared to be very water soluble. The hydrolysis product, when treated with phenacyl bromide,² yielded a compound melting at 220°C after two recrystallizations, indicating the presence of the sodium salt of a carboxylic acid in the hydrolysis product:





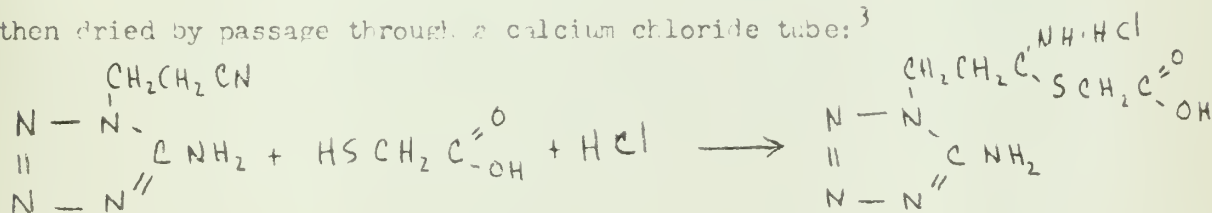
(2) Since the free acid of the previous hydrolysis was not isolated, it was decided to carry out a hydrolysis using an accurately weighed quantity of the pure compound resulting from (1), Section II, while following the pH closely throughout the hydrolysis. Standard base was added in half milliliter increments to the compound until the pH of the solution as measured by a comparator rose temporarily above a value of eleven, thereafter base was added two drops at a time until a permanent rise in pH above eleven was observed. This procedure required two days and yielded a value of molecular-weight for the compound equivalent to the expected formula:



Formula Weight = 138.14
Determined 137

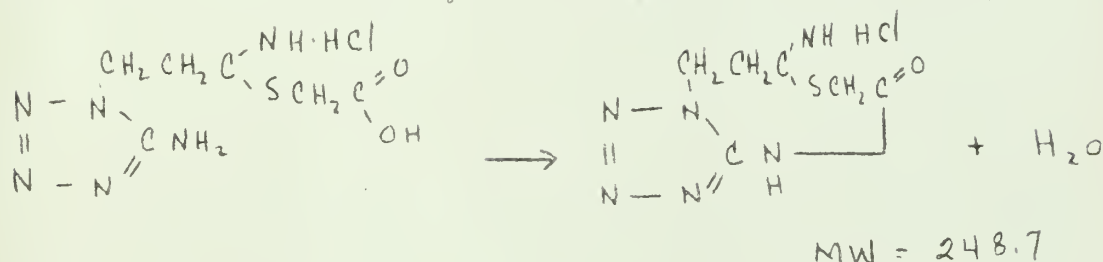
(3) The compound gave a positive Hinsberg test for primary amine and reacted with benzoyl chloride to give a compound melting at 178-180° after two recrystallizations, indicating that the compound was a primary amine.

(4) In an attempt to gain further confirmation of the molecular weight, one gram of the compound was placed in dry ether along with two grams of thioglycolic acid and the mixture was treated with dry hydrogen chloride which was generated by the action of sulfuric acid on calcium chloride and then dried by passage through a calcium chloride tube:³



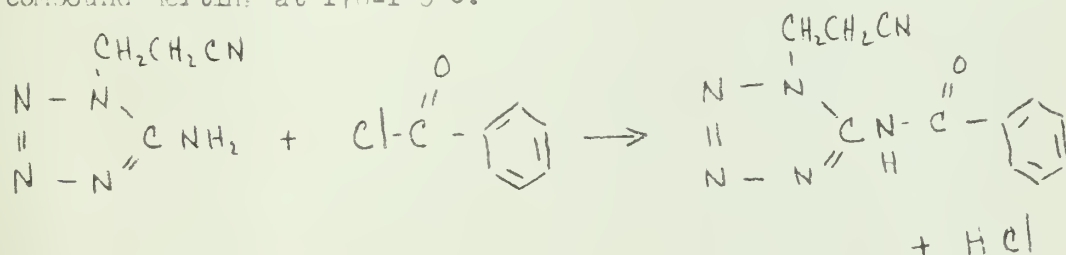
The resulting compound, obtained in good yield, was filtered, washed with cold ether, and placed in a vacuum desiccator containing sulfuric acid in

the bottom and paraffin and potassium hydroxide in the top to remove the last traces of acid and ether. After twenty-four hours in the desiccator, the compound was titrated with standard base and gave a neutralization equivalent of 248 instead of the expected 133 ($\frac{1}{2}$ of 266.7 since the product should have acted as a dibasic acid). This behavior is possible if one considers the possibility of the formation of a lactam ring:



This would account for the monobasic character and the discrepancy of 18 (H_2O).

(5) One gram of the suspected monosubstituted product was placed in a flask with one gram of benzoyl chloride and twenty milliliters of dry benzene and the mixture refluxed for fifteen minutes. Upon cooling, a quantity of crystals were obtained which upon recrystallization yielded a compound melting at 178-180°C.



The purpose of this reaction was to attempt to find a compound which upon hydrolysis of the nitrile group would give an acid which might be isolated for a molecular weight determination.

(6) No product was obtained with the attempted reaction of the compound with phenyl isothiocyanate.

(7) Next attempts to isolate and characterize a compound from the oil



resulting from the extended reaction of the 5-amino tetrazole and acrylonitrile were carried out. Many attempts were made to isolate a pure compound from the oil.

These attempts included:

(a) an attempted vacuum distillation, which resulted only in the decomposition of the product before any distillate was obtained. (N-substituted products of cyanoethylation characteristically decompose near their boiling points).¹

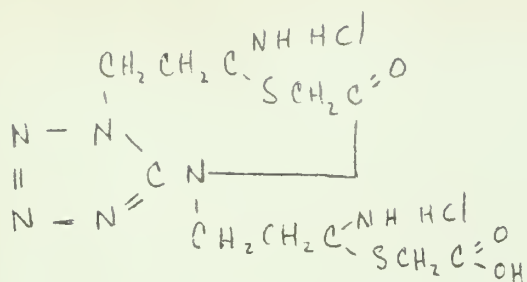
(b) construction of a simple molecular still utilizing an outer vacuum jacket and an inner finger filled with dry ice and acetone and separated a distance of one-half centimeter from the oil within the outer jacket. Use of this apparatus resulted in no appreciable separation.

(c) extraction with various solvents. Ethylene dichloride extraction yielded a clear, colorless oil which may have been a relatively pure compound.

Reactions carried out in an attempt to identify a compound from the oil follow:

- (1) Formation of a picrate. No crystals were obtained when a portion of the oil was heated with a saturated solution of picric acid in ethanol.
- (2) No crystals were obtained when an attempt was made to react a portion of the oil with methyl iodide to give the quaternary ammonium salt.
- (3) The basic hydrolysis of the oil yielded ammonia and an acid.
- (4) Reaction of the oil with thioglycolic acid and dry hydrogen chloride yielded a solid which, after 24 hours in the vacuum desiccator gave a neutralization equivalent of 147. This is equivalent to the compound:





(5) An attempt to react the oil with benzoyl chloride yielded no crystalline product.

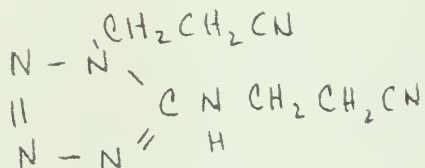
IV INTERPRETATION AND SUGGESTIONS

Based upon the evidence of the previous section, it would seem reasonably safe to conclude that 5 amino tetrazole adds to one molecule of acrylonitrile readily under the influence of a quaternary ammonium hydroxide catalyst and therefore that the compound obtained in (4) of section II has the formula:



Since facilities for an elemental analysis were not available, none was accomplished, however, this would be a deciding factor in the characterization if means were at hand to obtain such an analysis.

As for the compound resulting from addition to two molecules of acrylonitrile:



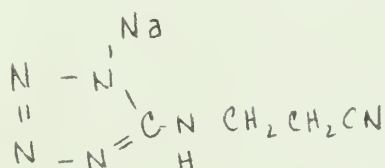
the reaction with thioglycolic acid and hydrogen chloride points to its presence in the oil, but is not conclusive. The fact that no reaction typical of primary amines could be accomplished with the oil is indicative of some change in the amine group.

In connection with attempts to form the dicyanoethylated product, where the reaction product is an oil instead of crystalline, it would be immensely helpful to have available an instrument such as the infrared spectrophotometer to give a quick indication of the introduction of new functional groups into the molecule.

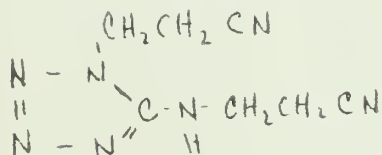


More reactions might be carried out, such as attempting to derivatize the oil to give a solid compound by attacking the amine group, then hydrolysing the -CN group to an acid and thereby obtaining a compound from which a molecular weight determination might be made.

The oil obtained from (9) Section II by reacting the sodium salt of 5 amino tetrazole with acrylonitrile and isolating the product through the silver salt indicates that the compound:



is formed by the reaction. Reaction of the free acid with another molecule of acrylonitrile should easily give the compound:



A molecular weight determination might be achieved by recovering the silver sulfide from the treatment of an accurately weighed sample of the silver salt with hydrogen sulfide.

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